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Long-Term (Three-Year) Prognosis of Patients Treated With Reperfusion or Conservatively After Acute Myocardial Infarction

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OBJECTIVES This survey sought to assess the frequency of the use of thrombolytic therapy, invasive coronary procedures (ICP) (angiography, percutaneous transluminal coronary angioplasty and coronary artery bypass grafting [CABG]), variables associated with their use, and their impact on early (30-day) and long-term (3-year) mortality after acute myocardial infarction (AMI).

BACKGROUND Few data are available regarding the implementation in daily practice of the results of clinical trials of treatments for AMI and their impact on early and long-term prognosis in unselected patients after AMI.

METHODS A prospective community-based national survey was conducted during January–February 1994 in all 25 coronary care units operating in Israel.

RESULTS Among 999 consecutive patients with an AMI (72% men; mean age 63 ± 12 years) acute reperfusion therapy (ART) was used in 455 patients (46%; thrombolysis in 435 patients [44%] and primary angioplasty in 20 [2%]). Its use was independently associated with anterior AMI location and hospitals with on-site angioplasty facilities, whereas advancing age, prior myocardial infarction (MI) and prior angioplasty or CABG were independently associated with its lower use. The three-year mortality of patients treated with ART was lower than in counterpart patients (22.0% vs. 31.4%, p = 0.0008), mainly as the result of 30-day to 3-year outcome (12.4% vs. 21.1%; hazard ratio = 0.73, 95% confidence interval [CI] 0.52 to 1.03). Independent predictors of long-term mortality were: age, heart failure on admission or during the hospitalization, ventricular tachycardia or fibrillation and diabetes. The outcome of patients not treated with ART differed according to the reason for the exclusion, where patients with contraindications experienced the highest three-year (50%) mortality rate. After ART, coronary angiography, angioplasty and CABG were performed in-hospital in 28%, 12% and 5% of patients, respectively. Their use was independently associated with recurrent infarction or ischemia, on-site catheterization or CABG facilities, non–Q-wave AMI and anterior infarct location. In the entire study population, and in patients with a non–Q-wave AMI, performance of ICP was associated with lower 30-day mortality (odds ratio [OR] = 0.53, 95% CI 0.25 to 0.98, and OR = 0.21, 0.03 to 0.84, respectively), but not thereafter.

CONCLUSIONS This survey demonstrates the extent of implementation in daily practice of ART and ICP and their impact on early and long-term prognosis in an unselected population after AMI. (J Am Coll Cardiol 1999;34:70–82) © 1999 by the American College of Cardiology

Several large-scale randomized clinical trials in patients with acute myocardial infarction (AMI) have demonstrated that thrombolytic therapy reduces mortality early after AMI (1). However, these studies failed to demonstrate an extra benefit after hospital discharge (2). Other randomized studies evaluating the physiologic effectiveness of thrombolytic therapy demonstrated extended long-term mortality benefit of early successful complete reperfusion (Thrombolysis in Myocardial Infarction [TIMI] grade 3 flow) (3,4), which may be related to improved left ventricular function at the time of hospital discharge (3–5). Recently, several moderate-sized randomized studies have reported that primary percutaneous transluminal coronary angioplasty without antecedent thrombolytic therapy may improve prognosis after AMI (6).

Although randomized trials are the preferred method for assessing therapeutic modalities, useful information can also be gained from prospective registry data which demonstrate

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Abbreviations and Acronyms

AMI	= acute myocardial infarction
ART	= acute reperfusion therapy
CABG	= coronary artery bypass grafting
CCU	= coronary care unit
CI	= confidence interval
ECG	= electrocardiogram
HR	= hazard ratio
ICP	= invasive coronary procedures
MI	= myocardial infarction
NQWMI	= non–Q-wave myocardial infarction
OR	= odds ratio
TIMI	= Thrombolysis in Myocardial Infarction
tPA	= tissue-type plasminogen activator

to what extent therapeutic measures like acute reperfusion therapy (ART) (thrombolysis or primary angioplasty) and invasive coronary procedures (ICP) (angiography, nonprimary angioplasty and coronary artery bypass grafting [CABG]) were implemented in daily practice in unselected AMI patients hospitalized in coronary care units (CCUs). Such an assessment on a national basis has seldomly been conducted (7–10).

The purpose of the present study was to determine the clinical practice pattern of the use of thrombolysis, ICP and medical management of unselected patients with AMI, in a prospective, observational national survey conducted in all CCUs in Israel, in 1994, and their impact on in-hospital complications and short- (30-day) and long-term (three-year) prognosis.

METHODS

Patient population. A nationwide prospective survey was performed during a two-month period (January and February 1994) in all 25 CCUs operating in Israel, as described elsewhere (11). In brief, demographic, historical and clinical data including in-hospital complications, medical management and procedures performed were collected on specific forms for all participants by dedicated study physicians in the CCUs. The diagnosis of AMI was based on clinical, electrocardiographic and enzymatic findings. Eligibility for inclusion in the survey was validated before discharge from the CCU. Thrombolytic therapy was used at the discretion of each center. Reasons for not utilizing thrombolytic therapy were recorded. In patients with more than one reason for exclusion from thrombolytic therapy, one reason was selected after completion of the survey on the basis of the following scale of priority: 1) contraindication to thrombolysis; 2) unqualifying electrocardiogram (ECG); 3) late arrival; and 4) other reasons (i.e., advanced age, nonspecific symptoms, death before decision was taken and spontaneous reperfusion). There were no uniform guidelines for the use of coronary arteriography, angioplasty or CABG, but most of the centers used a "conservative strategy" of "watchful waiting" with coronary arteriography followed by coronary mechanical reperfusion (12). On-site catheterization and CABG facilities were available in 19 and 11 of the centers, respectively.

Thirty-day and three-year mortality rates were assessed for all patients participating in the survey from hospital charts and by matching the identification numbers of the patients with the Israeli National Population Register.

Statistical analysis. All analyses were performed using SAS (Cary, North Carolina) statistical software. Chi-square and *t* tests were used to determine the significance of the differences between proportions and mean values, respectively. Results of continuous variables are reported as mean ± 1 SD. The nonparametric Wilcoxon test was used to compare the time from pain onset to thrombolytic therapy in the different groups. Two-sided p values are reported.

Stepwise logistic regression analyses (SAS LOGISTIC Procedure) were performed to assess potential variables associated with the use of ART (thrombolysis or primary angioplasty) and ICP (angiography, nonprimary angioplasty and CABG) during the hospitalization period.

Survival curves were estimated by use of the Kaplan-Meier method. The significance of the difference between the survival curves was assessed by the log-rank test (SAS LIFETEST Procedure).

Primary risk models were constructed to determine variables independently associated with mortality. Gender and ART were added to the best model selected if they were not significant, in order to determine their prognostic significance. For 30-day mortality a stepwise logistic regression analysis (SAS LOGISTIC Procedure) was used, and for three-year mortality in 30-day survivors and cumulative three-year mortality, Cox proportional-hazard regression models (SAS PHREG Procedure) were used. In all stepwise procedures, a variable was allowed to entered into the model if it made a significant contribution at the 0.15 level, and was removed if after subsequent addition of other variables, it no longer made a contribution at the 0.10 level.

RESULTS

Patients' Characteristics

During the survey period, 999 patients (721 men, 72%, mean age 63.4 ± 12.2 years) were hospitalized for AMI. Of them 455 patients (46%) received ART (thrombolysis 435 patients [44%] and primary angioplasty 20 patients [2%]) and 544 patients did not. The baseline characteristics of both groups are presented in Table 1.

Acute Reperfusion Therapy

Thrombolysis. Thrombolytic therapy was used in 435 patients. Streptokinase was the most common thrombolytic agent used (85%); tissue-type plasminogen activator (tPA) or other thrombolytic agents were used in 4% and 11%,

Table 1. Baseline Characteristics of Patients Treated or Not Treated by Acute Reperfusion (Thrombolysis or Primary Angioplasty)

	Acute Reperfusion		
	Yes* (n = 455)	No (n = 544)	p Value
Age (yr) (mean ± SD)	61.3 ± 11.9	65.2 ± 12.2	< 0.0001
Range (yr)	23–88	29–92	
≥65 yr	189 (42)	314 (58)	< 0.0001
Male gender	347 (76)	374 (69)	0.008
History of			
Angina	101 (22)	154 (28)	0.027
CHF	18 (4)	82 (17)	< 0.0001
Prior MI	101 (22)	189 (35)	< 0.0001
CABG/angioplasty	16 (4)	45 (8)	0.002
Diabetes	116 (25)	165 (30)	0.09
Hypertension	181 (40)	237 (44)	0.23
Hyperlipidemia	108 (24)	135 (25)	0.69
CVA	17 (4)	39 (7)	0.019
Family history	63 (14)	68 (13)	0.53
Smoking	187 (41)	180 (33)	0.009
MI location			
Anterior	235 (52)	252 (46)	< 0.0001
Inferior/posterior	205 (45)	213 (39)	
Lateral	12 (3)	49 (9)	
Undetermined	3 (1)	30 (6)	
Q_wave	359 (79)	284 (52)	< 0.0001
Killip class ≥II on admission	127 (28)	198 (36)	0.004
Peak CK (IU)	1,605 ± 1,880	947 ± 1,315	< 0.0001

*Thrombolysis in 435 patients, and primary angioplasty in 20.

CABG = coronary artery bypass grafting; CHF = congestive heart failure; CK = creatine kinase; CVA = cerebrovascular accident; MI = myocardial infarction.

respectively. In-hospital thrombolytic therapy was started in the CCU setting in 79% of the cases, in the emergency room in 16% and in other departments in 4%. In only 1.5% of the cases prehospital thrombolytic therapy was initiated in the mobile CCU setting. The median time from pain onset to thrombolysis (reported for 83% of thrombolysed patients [n = 361]) was 2.5 h (mean 3.1 ± 2.2 h). This time distribution was <1.5 h: 22% of the patients; 1.5 to 3 h: 46%; 3.5 to 6 h: 27%; and >6 h: 5% of the patients. This time interval was slightly longer in women than in men (median time 3.0 vs. 2.5 h, respectively, p = 0.17), and with advancing age (median time for age <55 years: 2 h; 55 to 64 years: 2.5 h; 65 to 74 years: 3 h; and for age >75 years: 3 h; p = 0.14).

Primary angioplasty. Primary angioplasty was performed in 20 patients (2%), in 10 of the 19 centers with catheterization facilities; 12 cases were performed in three centers, and the other eight cases in seven centers. The main reason for performing primary angioplasty was contraindication to thrombolysis (eight patients, 40%). The patients' baseline characteristics, including Killip class on admission (class I, 14 patients [70%]), were similar to those of patients who underwent thrombolysis. None of these patients had a subsequent angioplasty or CABG during the hospitalization course.

During the survey period, 544 patients (54%; 52% of men and 61% of women, p = 0.008) were excluded from ART. Of them, 474 patients (87%) had only one reason for exclusion, and 70 patients (13%) had ≥2 reasons. The main reason for exclusion from ART was unqualifying ECG (234 patients [23%]). Other reasons were: late arrival (129 patients [13%]), contraindication (114 patients [11%]) and other reasons (67 patients [7%]). There was no difference in the proportion of these reasons between men and women.

Variables Associated With Acute Reperfusion Therapy Use

The proportion of patients treated with ART declined significantly with advancing age (age <55 years: 54%; 55 to 64: 53%; 65 to 74: 39%, and ≥75 years old: 34%; p for trend <0.0001; Table 2). Women were treated with ART less frequently than men (39% vs. 48%, respectively, p = 0.008). However, the difference was of borderline statistical significance after multivariate adjustment (Table 2). Prior angioplasty or CABG were independently associated with lower use of ART, whereas anterior infarct location and hospitalization in a center with on-site catheterization facilities were associated with its increased use (Table 2).

Invasive Coronary Procedures During the Index Hospitalization

Coronary angiography. After ART, subsequent in-hospital coronary angiography (not including 20 patients with primary angioplasty) was performed in 271/979 patients (28%). Of them 164 patients (61%) underwent angioplasty or CABG during the index hospitalization (Table 3). Coronary arteriography use was irrespective of whether the patients received thrombolysis or not (Tables 2 and 3). Its use significantly declined with advancing age (age <55 years: 38%; 55 to 64: 27%; 65 to 74: 25%, and ≥75 years old: 11%; p for trend <0.0001; Table 2), and was lower in women than in men (21% vs. 28%, respectively, p < 0.0001). However, after multivariate adjustment the lower use of coronary angiography in women was not of statistical significance (Table 2). Recurrent myocardial infarction (MI) or recurrent ischemia, hospitalization in centers with catheterization facilities, anterior infarct location and non–Q-wave MI (NQWMI) were independently associated with the use of coronary arteriography, whereas Killip class ≥II on admission, a history of cerebrovascular event and diabetes were associated with its lower use (Table 2).

Angioplasty. After ART, subsequent angioplasty (not including 20 patients with primary angioplasty) was performed in 118/979 patients (12%). It was performed more frequently in patients initially treated with thrombolysis (15% vs. 9%, p = 0.004; Table 3). However, after adjustment, performance of angioplasty during the index hospitalization was not associated with thrombolysis use (Table

Table 2. Variables Associated With the Use of Acute Reperfusion, Coronary Angiography, Angioplasty and CABG

Variables	Procedure			
	Acute Reperfusion* (n = 455), OR (95% CI)	Angiography (n = 271), OR (95% CI)	Angioplasty (n = 118), OR (95% CI)	CABG (n = 46), OR (95% CI)
Age (10-yr increments)	0.89 (0.72–0.91)	0.73 (0.63–0.84)	0.66 (0.55–0.79)	0.87 (0.67–1.12)
Female gender	0.77 (0.56–1.06)	0.89 (0.60–1.31)	1.30 (0.78–2.13)	0.60 (0.25–1.27)
Prior MI	0.64 (0.47–0.87)	—	—	—
Prior angina	—	1.67 (1.16–2.41)	—	—
Prior CABG or PTCA	0.47 (0.25–0.86)	—	—	—
Killip class ≥II on admission	—	0.39 (0.26–0.59)	0.26 (0.13–0.48)	—
Prior CVA	—	0.33 (0.12–0.78)	—	—
Anterior location	1.27 (0.98–1.65)	1.47 (1.07–2.04)	1.53 (1.01–2.31)	—
Non–Q-wave MI	†	1.96 (1.41–2.70)	—	2.50 (1.35–4.76)
On-site hospital facilities	1.79 (1.34–2.40)‡	2.45 (1.60–3.84)‡	1.52 (0.94–2.55)‡	3.61 (1.73–8.50)§
Diabetes	—	0.70 (0.47–1.02)	0.63 (0.36–1.04)	—
Recurrent MI/ischemia	†	7.35 (4.73–11.59)	5.09 (3.11–8.29)	2.85 (1.38–5.61)
Acute reperfusion	†	—	—	—

*Thrombolysis or primary angioplasty. †Was not included in the analysis; — Did not enter into the model in the stepwise procedure. On-site hospital facilities were considered: ‡hospitals with catheterization facilities; §hospitals with CABG operation facilities (OR = 1). Each column represents the ORs for variables selected as significant predictors in the stepwise logistic analysis.

CI = confidence interval; OR = odds ratio. Other abbreviations as in Table 1.

2). Other variables associated with the use of angioplasty are presented in Table 2.

Coronary artery bypass grafting. The use of CABG during the index hospitalization was low in this survey (46 patients, 5%). Its use was similar in patients treated with ART and in their counterparts (Table 3). On-site CABG operation facilities, recurrent MI or recurrent ischemia and NQWMI were independently associated with increased use of CABG operation (Table 2).

In-Hospital Medications

Patients treated with ART more frequently received heparin, aspirin and beta-adrenergic blocking agents, and less frequently received diuretics and digitalis, as compared with their counterparts (Table 3). The use of other medication was similar in both groups.

In-Hospital Complications

Patients treated with ART more frequently experienced ventricular tachycardia (all types) or fibrillation, bleeding complications and recurrent infarction, and less frequently experienced paroxysmal atrial flutter/fibrillation and congestive heart failure than their counterparts (Table 3).

Mortality

The 30-day, 30-day to 3-year and 3-year cumulative mortality rates for the patients who participated in the survey were: 12.1%, 17.1% and 27.1%, respectively. Mortality increased significantly with advancing age (Fig. 1, Table 4). Women fared worse than men, with higher 30-day (23.7% vs. 10.0%, p = 0.009) and 30-day to 3-year crude mortality rates (36.0% vs. 17.6%, p = 0.015). However, after adjustment, the odds ratio for death in women as compared with men was of borderline significance at 30 days, but not thereafter (Table 4). Other variables independently associated with increased mortality are presented in Table 4. Use of ICP was associated with decreased 30-day mortality (odds ratio [OR] 0.53), but not thereafter. Hospitalization in centers with on-site catheterization facilities was not associated with lower mortality.

The 30-day, 30-day to three-year and three-year crude mortality rates were lower in patients treated with ART as compared with counterpart patients, but reached statistical significance only after 30 days (Table 3, Fig. 2). After multivariate adjustment (Table 4), patients receiving ART had a similar 30-day mortality as their counterparts (OR 0.96, 95% confidence interval [CI] 0.60 to 1.54), but a lower mortality thereafter with a difference that amplified after 30 days through 3 years (hazard ratio [HR] 0.73, 95% CI 0.52 to 1.03).

The outcome of patients excluded from ART (i.e., contraindication, unqualifying ECG, late arrival and other reasons) differed according to the reason for exclusion (Table 5, Fig. 3). Patients excluded from ART (mainly thrombolysis) because of contraindications (n = 114) had the highest 30-day (OR 1.78) and three-year mortality rates (HR 1.71). In patients excluded from ART because of late arrival (n = 129) or other reasons (n = 67), the 30-day and the three-year mortality rates did not differ significantly from patients treated with ART. On the other hand, patients with an unqualifying ECG (n = 234) had a lower 30-day mortality rate (OR 0.47), but an increased 30-day to three-year mortality (HR 1.50) as compared with patients who underwent ART. In this latter group, 153/234 patients (65%) had a NQWMI.

Table 3. In-Hospital Invasive Coronary Procedures, Medications, Complications and Mortality of Patients Treated or Not Treated by Acute Reperfusion

	Acute Reperfusion		
	Yes (n = 455)	No (n = 544)	p Value
Invasive coronary procedures			
Angiography*	132 (30)	139 (26)	0.10
Angioplasty*	67 (15)	51 (9)	0.004
CABG	19 (4)	27 (5)	0.55
Medications			
IV heparin	401 (88)	374 (69)	< 0.0001
Aspirin	407 (90)	424 (78)	< 0.0001
Nitrates	367 (81)	433 (80)	0.68
ACE-I	155 (34)	210 (39)	0.14
Beta-blockers	218 (48)	209 (38)	0.003
Calcium antagonists	95 (21)	124 (23)	0.47
Digitalis	38 (8)	64 (12)	0.08
Diuretics	119 (26)	194 (36)	0.001
Complications			
VT/VF	82 (18)	47 (9)	< 0.0001
II° III° AV Block	42 (9)	39 (7)	0.23
PAF	26 (6)	63 (12)	0.001
CHF	66 (15)	113 (21)	0.01
Cardiogenic shock	33 (7)	34 (6)	0.53
Bleeding	22 (5)	6 (1)	0.0004
Recurrent MI	23 (5)	6 (1)	0.001
Recurrent ischemia	45 (10)	53 (10)	0.94
Rupture/VSD	6 (1.3)	2 (0.6)	0.20
Stroke	5 (1.1)	3 (0.6)	0.33
Mortality			
30-day	50/455 (11.0)	71/544 (13.1)	0.32
1-year cumulative	68/455 (15.0)	122/544 (22.4)	0.004
3-year cumulative	100/455 (22.0)	171/544 (31.4)	0.0008
30-day to 3-year	50/405 (12.4)	100/473 (21.1)	0.0006

*Out of 435 patients (not including 20 patients who underwent primary PTCA).
ACE-I = angiotensin-converting enzyme inhibitors; AV = atrioventricular; IV = intravenous; PAF = paroxysmal atrial flutter/fibrillation; VF = ventricular fibrillation; VT = ventricular tachycardia; VSD = ventricular septal defect. Other abbreviations as in Table 1.

Non–Q-Wave Infarction

A NQWMI was noted in 356 patients. The baseline characteristics, management and in-hospital complications of NQWMI patients treated with an early ICP (n = 124) or conservatively (n = 232) are presented in Table 6. Patients treated with ICP were younger, and had anterior infarct location more often and a better Killip class on admission. Other baseline characteristics of both groups were comparable. The ICP group patients were treated with thrombolysis, heparin, aspirin, nitrates and beta-blockers more often, and with digitalis and diuretics less often. The ICP group experienced recurrent AMI or ischemia more often (fourfold) than their counterpart group. The prognosis of NQWMI patients treated or not with ICP differed (Table 6, Fig. 4). The 30-day (1.6% vs. 9.9%, p = 0.004), 30-day to 3-year (15.6% vs. 23.9%, p = 0.07) and cumulative three-year crude mortality rates (16.9% vs. 31.5%, p = 0.003) were lower in the former. However, after adjustment for age, gender, history of diabetes, angina, prior MI, anterior infarct location, congestive heart failure on admission (Killip class ≥II) or during the hospitalization course, ventricular tachycardia or fibrillation, ART and hospitalization in a center with on-site coronary catheterization facilities, performance of early ICP in patients with NQWMI was associated with lower 30-day mortality (OR 0.21, 95% CI 0.03 to 0.84), but not thereafter from 30 days to 3 years (HR 1.01, 95% CI 0.47 to 2.15). Hospitalization in a center with on-site coronary catheterization facilities was not associated with early (OR 0.98, 95% CI 0.37 to 2.94) or long-term outcome (HR 1.01, 95% CI 0.47 to 2.15).

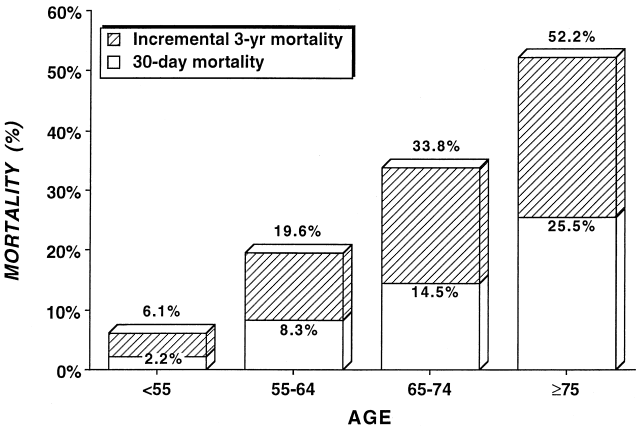

Figure 1. Thirty-day and three-year crude mortality rates by age subgroups (p for trend <0.0001, for both 30-day mortality and incremental three-year mortality rates).

DISCUSSION

In the present survey, reflecting the clinical practice of the medical community at large in an unselected AMI population hospitalized in all CCUs operating in Israel, in 1994, half of the patients received ART (mainly thrombolysis). Acute reperfusion therapy was associated with decreased three-year mortality (22.0% vs. 31.4%, p = 0.0008), mainly as the result of 30-day to three-year outcome (12.4% vs. 21.1%; HR 0.73). Patients excluded from ART because of contraindication carried the worst prognosis (twofold risk as compared with patients treated with ART). After ART, subsequent use of ICP during the index hospitalization course was relatively low (28%), reflecting the "conservative strategy" of "watchful waiting" with coronary arteriography (12). Variables independently associated with ICP use were recurrent infarction or ischemia, on-site catheterization or CABG facilities, NQWMI and anterior infarct location. Performance of ICP was associated with lower 30-day mortality in the entire study population (OR 0.53) and in patients with a NQWMI (OR 0.21), but not thereafter.

Table 4. Multivariate Stepwise Logistic Regression Analyses to Predict 30-Day, 30-Day to Three-Year and Three-Year Cumulative Mortality

Predictors	Mortality		
	30-Day, OR* (95% CI)	30-Day to 3-Year, HR† (95% CI)	3-Year Cumulative, HR† (95% CI)
Age (10-yr increments)	1.69 (1.34–2.16)	1.83 (1.53–2.18)	1.73 (1.52–21.98)
Female gender	1.39 (0.88–2.20)	0.93 (0.66–1.31)	1.11 (0.86–1.643)
Diabetes	1.81 (1.15–2.84)	2.30 (1.65–3.19)	2.04 (1.60–2.61)
Q-wave MI	2.22 (1.33–3.81)	—	—
Killip ≥II on admission or CHF during hospitalization	6.96 (4.06–12.56)	2.06 (1.47–2.90)	2.98 (2.26–3.94)
VT/VF	3.03 (1.77–5.16)	—	1.88 (1.37–2.57)
Invasive coronary procedures‡	0.53 (0.27–0.98)	—	—
Acute reperfusion	0.96 (0.60–1.54)	0.73 (0.52–1.03)	0.87 (0.68–1.24)

*Variables included in the stepwise logistic regression analysis were: age, history of diabetes, angina, prior MI, anterior infarct location, Q-wave infarction during the index hospitalization, congestive heart failure on admission (Killip class ≥II) or during the hospitalization course, ventricular tachycardia or fibrillation, invasive coronary procedures during the hospitalization course and hospitalization in a center with on-site coronary catheterization facilities. Acute reperfusion and gender were added to the best model selected. †By Cox proportional-hazard regression model, including the same variables. ‡Performance of either coronary angiography or angioplasty (not including primary angioplasty) or CABG during the hospitalization course. HR = hazard ratio. Other abbreviations as in Tables 1 to 3.

Thrombolytic therapy. In this community-based nationwide survey 44% of patients received thrombolytic therapy according to the discretion of each center. Similar rates of thrombolysis use were reported from Canada (13) and New Zealand (14). Higher rates were reported in Germany (52%) (9), in the United Kingdom (72%) among patients with final diagnosis of definite AMI (15) and in selected patients eligible for participation in randomized trials, such as those studied in the GISSI-3 (16) and the ISIS-4 (17) trials (≈70%) carried out in Europe. A lower rate of thrombolysis use (32%) was recently reported by the French AMI Survey in 1995 (10) and from 11 countries in Europe, in 1993–1994 (36%; ranging from 13% to 52%) (18). In the U.S. as compared with Europe, lower figures (23% to 35%) have been recorded (7,8,19–22).

In the current survey streptokinase was the most common thrombolytic agent used (85%), similar to other places in Europe (9,17,18) and dissimilar to the U.S. practice, where the most common thrombolytic agent used is tPA (≈70%) (7,21). This practice relates to the lower cost of streptokinase as compared with tPA, and the use of the latter in selected cases where its benefit was proven, that is, non-

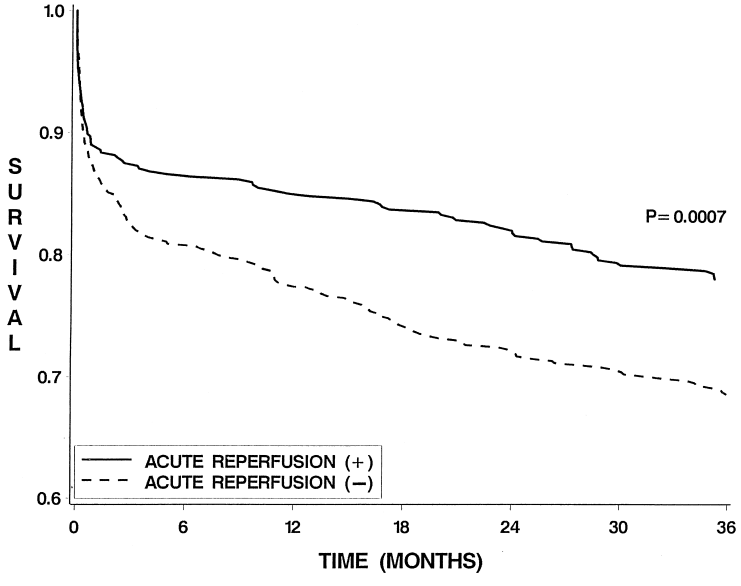

Figure 2. Three-year Kaplan-Meier cumulative survival curves for patients who underwent acute reperfusion and those who did not; differences were assessed by log-rank test; p = 0.0007.

Table 5. Crude and Adjusted Mortality Rates of Patients Treated or Not Treated by Acute Reperfusion by Reason for Exclusion

	Mortality					
	30-Day		30-Day to 3-Year		3-Year Cumulative	
Group of Patients	n (%)	OR* (95% CI)	n (%)	HR* (95% CI)	n (%)	HR* (95% CI)
Acute reperfusion (n = 455)	50 (11.0)	1.0	50 (12.4)	1.0	100 (22.0)	1.0
No acute reperfusion because of						
Contraindication (n = 114)	33 (28.9)	2.07 (1.14–3.37)	24 (29.6)	1.78 (1.09–2.92)	57 (50.0)	1.71 (1.23–2.38)
Unqualifying ECG (n = 234)	12 (5.1)	0.47 (0.22–0.97)	48 (21.6)	1.50 (1.01–2.24)	60 (25.6)	0.96 (0.69–1.34)
Late arrival (n = 129)	15 (11.7)	0.76 (0.36–1.53)	18 (15.8)	0.96 (0.56–1.66)	33 (25.6)	0.91 (0.61–1.35)
Other reasons (n = 67)	11 (16.4)	1.14 (0.48–2.55)	10 (17.9)	1.11 (0.56–2.20)	21 (31.3)	1.16 (0.72–1.87)
†p value	< 0.0001		0.12		< 0.0001	
‡p value	< 0.0001		0.001		< 0.0001	

*The odds ratio (OR) or hazard ratio (HR) of not undergoing acute reperfusion (thrombolysis or primary angioplasty) because of contraindication, unqualifying electrocardiogram (ECG), late arrival or other reasons as compared with patients who underwent acute reperfusion (reference group) by multivariate analyses adjusting for variables selected in Table 4. †p value for differences between crude mortality rates among the four groups of patients who did not undergo acute reperfusion. ‡p value for differences between crude mortality rates among all groups.

elderly patients presenting within 3 h from symptoms onset with anterior AMI (23).

The median time from symptom onset to thrombolysis was 2.5 h in this survey, slightly shorter than in other reports (7,9,12). Elderly and female patients received thrombolytic therapy later than their counterparts, similar to other reports (7,12,24). Thrombolysis was initiated in most cases in the hospital CCU (79%), in 16% in the emergency room and prehospital (mobile CCU) in only 1.5%. This low prehospital thrombolysis utilization rate is in accordance with reports from Europe (2.5%) (18), and in discordance with reports from the U.S. (7,21), and may be explained, in part, by the fact that most urban places in Israel are located at a reasonable distance from the nearby hospital and have a mobile CCU service. Thus, because of the rapidity of transportation, the direct transfer of many patients from the mobile CCU to in-hospital CCU, and the preference of cardiologists to initiate thrombolytic therapy in a hospital CCU setting, in most of the cases thrombolytic therapy was initiated in a hospital CCU.

Primary angioplasty. Primary angioplasty represents an alternative method for myocardial reperfusion (6). However, its use requires special facilities and a trained, experienced team of medical personnel. Fewer than 20% of hospitals in the U.S. and less than 10% of hospitals in Europe are able to meet these requirements (25). A similar situation exists in Israel, and despite the fact that 19 of the 25 CCUs have on-site catheterization facilities, primary angioplasty was rarely used (20 patients, 2%). A low rate of primary angioplasty use was also noted in a survey in Germany (1.4%) (9) and in the NRMI-1 (3.1%) (7) and NRMI-2

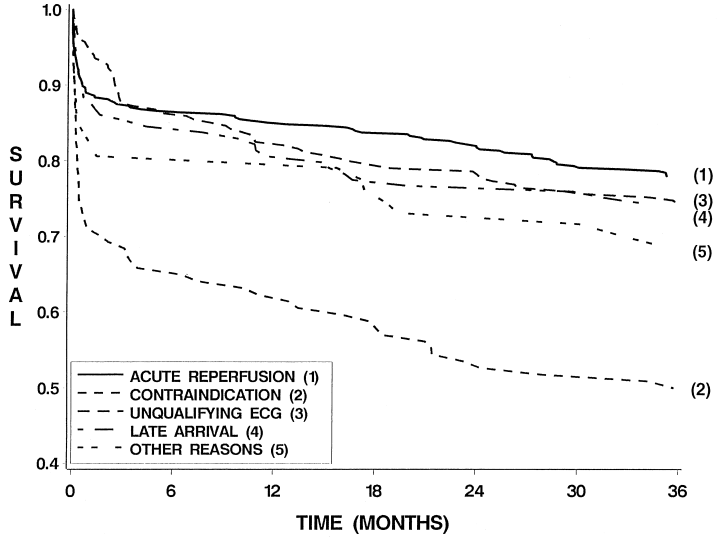

Figure 3. Three-year Kaplan-Meier cumulative survival curves for patients who underwent acute reperfusion and those who did not by reason of exclusion (contraindication, unqualifying electrocardiogram [ECG], late arrival and other reasons).

Table 6. Baseline Characteristics, Management, Complications and Mortality of 356 Patients with Non–Q-wave MI Treated or Not Treated by Invasive Coronary Procedures

	Invasive Coronary Procedure*		
	Yes (n = 124)	No (n = 232)	p Value
Age (yr) (mean ± SD)	59.5 ± 11.7	66.5 ± 11.5	< 0.0001
≥65 yr	47 (38)	142 (61)	< 0.0001
Male gender	96 (77)	155 (67)	0.04
History of			
Angina	40 (32)	69 (30)	0.62
Prior MI	37 (30)	90 (39)	0.08
CABG/angioplasty	8 (7)	27 (12)	0.12
Diabetes	25 (20)	62 (27)	0.17
Hypertension	51 (41)	104 (45)	0.50
Smoking	48 (39)	69 (30)	0.09
Anterior MI location	75 (60)	105 (45)	0.006
Killip class ≥II on admission	20 (16)	87 (38)	< 0.0001
Peak CK (IU)	681 ± 701	800 ± 918	0.18
Management			
Angioplasty	48 (39)	—	—
CABG	26 (21)	—	—
Thrombolysis	37 (30)	49 (21)	0.07
IV heparin	111 (90)	153 (66)	< 0.0001
Aspirin	109 (88)	182 (78)	0.03
Nitrates	107 (86)	169 (73)	0.004
ACE-I	43 (35)	81 (35)	0.96
Beta-blockers	70 (57)	92 (40)	0.002
Calcium antagonists	31 (25)	69 (30)	0.34
Digitalis	4 (3)	22 (10)	0.03
Diuretics	23 (19)	79 (34)	0.002
Complications			
VT/VF	5 (4)	20 (9)	0.11
PAF	6 (5)	24 (10)	0.07
CHF	10 (8)	26 (11)	0.35
Recurrent MI/ischemia	31 (25)	14 (6)	< 0.0001
Mortality			
30-day	2/124 (1.6)	23/232 (9.9)	0.004
1-year	14/124 (11.3)	50/232 (21.6)	0.02
3-year cumulative	21/124 (16.9)	73/232 (31.5)	0.003
30-day to 3-year	19/122 (15.6)	50/209 (23.9)	0.07

*Angiography, angioplasty or CABG, not including primary angioplasty. Abbreviations as in Tables 1 and 3.

surveys (3.9%) (8) in the U.S., whereas a higher rate of use was noted in the MITI Registry (8.5%) (21) and the French AMI Survey (13%) (10).

Factors associated with the use of acute reperfusion. In this survey, factors independently associated with the use of ART were anterior infarct location and on-site catheterization facilities. In patients with anterior infarction the risk of developing large infarction is greater than in counterpart AMI patients, hence there is a greater potential for myocardial salvage by either thrombolysis or primary angioplasty. This concurs with previous studies showing the greatest survival benefit with thrombolysis (1) or with primary angioplasty (6) in high risk patients, that is, anterior AMI. The independent association between use of ART and hospitalization in centers with on-site catheterization facilities (OR 1.75) indicates that in these centers as compared with centers without such facilities, a more aggressive reperfusion strategy with either thrombolysis (47% vs. 34%, respectively, $p < 0.001$) or primary angioplasty (2.6% vs. 0.4%, respectively, $p = 0.03$) is in use. This finding is in accordance with the GISSI-3 trial (26) and in discordance with the MITI Registry (20).

On the other hand, advanced age, prior infarction and prior angioplasty or CABG were independently associated with lower use of ART, whereas female gender had a borderline association. The independent association between advanced age and lower use of ART (mainly thrombolysis) is in accordance with other studies (7,8,19,20, 26,27). The progressive rise in the incidence of major hemorrhagic complications with increasing age formed the

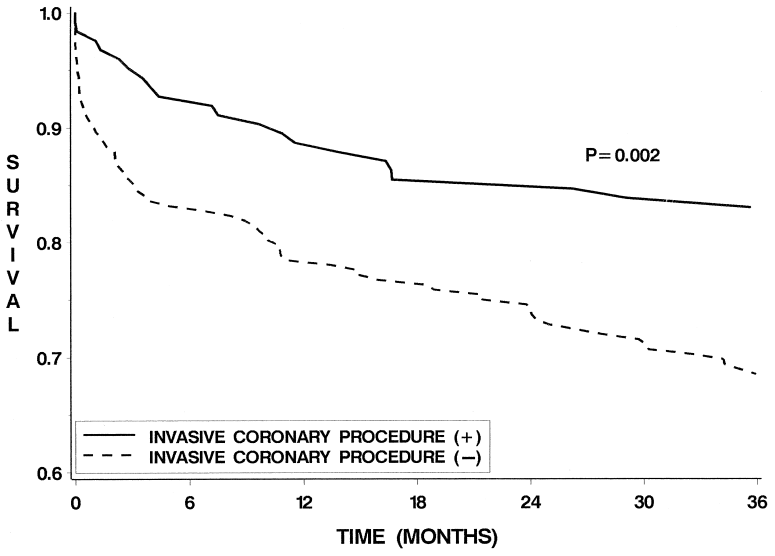

Figure 4. Three-year Kaplan-Meier cumulative survival curves for patients with non–Q-wave acute myocardial infarction who underwent invasive coronary procedures (angiography, angioplasty or coronary artery bypass grafting, not including primary angioplasty) and those who did not; p = 0.002, by log-rank test.

rationale for excluding patients aged ≥75 years from early thrombolytic trials (28). However, since ART by either primary angioplasty or thrombolysis is more efficacious in the elderly (1,29–31), its use should be advocated in elderly patients with AMI as well, unless specific contraindications are present.

The independent association between prior infarction and the lower use of ART may be explained, by the fact that in these patients the recognition of new infarction is more difficult. They often present with a non–ST-elevation AMI, and in about half of them the diagnosis of AMI is missed on admission (15). Among patients with prior CABG as compared with counterparts who did not undergo CABG, the lesion that produces infarction is more likely to be situated in a distal or branch vessel, and as a consequence infarct size determined by enzymatic assessment and ECG changes tends to be smaller, and may culminate in a NQWMI or even be obscured (32).

Women were treated with ART less frequently than men (39% vs. 48%, p = 0.008). This seemingly lower use of ART in women is related to their older age, other comorbid conditions and longer time interval from symptom onset to therapy, since after adjustment for age and other confounding variables this difference was of borderline statistical significance (OR 0.77, p = 0.11). Similar findings were noted in our earlier national AMI survey in 1992 (33), and in other studies (34,35), whereas in other studies the use of thrombolysis in women remained lower than in men even after adjustment (8,18,26,36).

Killip class ≥II on admission was not associated with the use of ART in this survey. In hemodynamically compromised patients, those with Killip class III on admission or with cardiogenic shock, emergent mechanical reperfusion by either angioplasty or CABG may be a more promising mode of reperfusion than thrombolysis (37). However, their use in our survey was low, and they were not exclusively performed in patients with shock. Among the 20 patients who underwent primary angioplasty, only one patient was in Killip class III on admission and two patients were in class IV. Two of these three patients (one in class III and one in class IV) died during the index hospitalization.

Determinants of the use of coronary angiography, angioplasty and CABG after acute reperfusion. After ART, subsequent use of ICP during the index hospitalization was relatively low (coronary angiography was performed in 28%, angioplasty in 12% and CABG in 5% of the patients), reflecting the "conservative strategy" of "watchful waiting" with coronary arteriography (7). Markedly higher rates were reported in the U.S., where more "invasive strategy" is in use (7,20,22,38–41). Interestingly, the variables independently associated with the use of ICP in both strategies were quite similar, and included recurrent ischemia or reinfarction (20,40), presence of NQWMI and anterior infarct location (40) and hospitalization in centers with on-site catheterization or CABG facilities (20,22,40,42). This finding indicates the heterogeneity of the use of these procedures, which in some centers were used more liberally. On the other hand, in this survey and in other studies, advancing age (20,40), Killip class ≥II on admission (20) and a history of stroke or transient ischemic attack (40) were independently associated with lower use of ICP. In these patients, performance of ICP carries an increased procedural risk, even though potentially elderly patients and patients with heart failure may benefit more from such procedures as compared with low risk patients. Diabetes was associated with lower

use of ICP in this survey but not in others (40,43). In contrast to other studies that noted an independent high use of ICP in patients treated with thrombolysis (7,20,44), this difference was not noted. Also we did not observe a lower use of ICP in women in the current survey, as well as in our previous survey in 1992 (32), in accordance with some (45) but discordant with others (8,20,36,46).

Mortality. In accordance with previous reports, powerful independent predictors of early and long-term mortality after AMI were age (8,9,12,13,20,47,48), heart failure on admission or during the hospitalization course (8,9,12,13, 47,48) and diabetes (8,47,49). Women fared worse than men, with higher early and long-term crude mortality rates. However, after adjustment for pertinent variables, the odds ratio for dying in women as compared with men was of borderline statistical significance at 30 days (OR 1.39; $p = 0.15$), but not thereafter, in accordance with other studies (47,50).

Acute reperfusion therapy was associated with a borderline early favorable prognosis (Fig. 2, Tables 3 and 4). Similar findings were noted in other AMI surveys as well (10,51) and in one randomized thrombolytic trial of streptokinase (52). In the French AMI Survey (10), five-day mortality was lower in patients reperfused by thrombolysis or primary angioplasty than in counterpart patients (8.2% vs. 5.6%); however, after multivariate adjustment this benefit disappeared. In the MITI Registry (51) in-hospital mortality was lower in patients treated with thrombolysis (6.7% vs. 10.7%), a difference that was no longer evident after age adjustment. In the ISAM study (52) 21-day mortality was similar in streptokinase-treated patients and in control subjects (5.2% vs. 6.5%, respectively). On the other hand, most thrombolytic-controlled trials found early survival benefit with thrombolytic therapy (1). This discrepancy may be related to the selection bias of favoring patients with low risk characteristics in thrombolytic randomized trials. This view is also supported by the fact that in the current survey the overall 30-day mortality rate of patients treated with ART was higher (11.0%) than that reported in placebo-controlled thrombolytic trials by the Fibrinolytic Therapy Trialist Collaborative Study Group for thrombolysed patients at 35 days (9.6%) (1). Another explanation for this early borderline beneficial effect may be related to the small sample size of our population, which lacked the power to detect small differences between patients treated or not with ART. In fact, in the current study, the relative reduction in 30-day mortality between patients treated or not with ART was 16% (11.0% vs. 13.1%, respectively). This reduction was similar to that observed by the Fibrinolytic Therapy Trialist Collaborative Study Group of 17% in thrombolysed versus nonthrombolysed patients (9.6% vs. 11.5%, respectively), which reached statistical significance because of a much larger sample size ($n = 58,600$). Indeed, it is claimed that in estimating the effect of treatment, power calculation suggests, that the thrombolysis effect in reducing overall mortality will not be detected until the population with AMI includes at least 20,000 patients (51).

Of interest is the fact that patients treated with ART had an extended mortality benefit as compared with counterpart patients that amplified after 30 days through 3 years (12.4% vs. 21.1%, respectively; HR 0.73; Tables 3 and 4, Fig. 4). Similar findings were recently published by the GUSTO angiographic substudy investigators (3). Patients who achieved normal (TIMI grade 3) flow in the infarct-related artery and early preservation of the left ventricular function had a significant survival advantage well beyond the 30 days through two years (3). On the other hand, our findings are in discordance with earlier placebo-controlled thrombolytic trials demonstrating no extra benefit after hospital discharge in thrombolysis-treated patients (2). This long-term survival benefit in our study may be related to the greater reduction of infarct size by earlier administration of thrombolytic therapy (53), the wider use in recent years of new therapeutic modalities including aspirin, beta-blockers, and angiotensin-converting enzyme inhibitors, better prevention of reocclusion and reinfarction, and revascularization procedures in selected cases, as compared with earlier placebo-controlled thrombolytic trials. Our data are not complete concerning all medical and mechanical therapies over the three-year period, but we have data concerning therapies during the index hospitalization. Patients treated with ART more often received aspirin, heparin and beta-blockers, medications associated with improved outcome, and less often received digitalis and diuretics, medications associated with worse outcome, as is also evident in a lower rate of the in-hospital complication of congestive heart failure. These findings suggest a better preserved left ventricular function in patients treated with ART, which culminated in a long-term survival benefit.

Patients not treated with ART (mainly thrombolysis) had a worse early and long-term outcome. However, the prognosis of these patients differed according to the reason for exclusion. Patients not treated with ART because of contraindication had the highest crude and adjusted early and long-term mortality rates (Table 5, Fig. 3). A similar finding was noted in our survey in 1992, among patients excluded from the GUSTO protocol because of contraindication (54). These patients may benefit from primary angioplasty (55).

Patients with unqualifying ECG had small infarctions of NQWMI type (67% of the patients), with a low early mortality rate (OR 0.47) increasing thereafter (HR 1.50) (Table 5), in accordance with cohorts in the prethrombolytic era (56,57). No survival advantage was noted in NQWMI patients when treated with ART (58). However, despite their smaller infarct size, they may experience higher rates of postinfarction ischemic events. Therefore, these patients may benefit from ICP when performed during the hospitalization course (59). This explains the higher (twofold) use of ICP in these patients as compared with counterparts with a Q-wave AMI (35% [124/356] vs. 23%

[147/643], p = 0.003, Table 2). Moreover, the prognosis of NQWMI patients treated or not with ICP differed, and the early and 3-year crude mortality rates were lower in the former (Table 6, Fig. 4). However, after adjustment, performance of early ICP in patients with NQWMI was associated with lower 30-day mortality (OR 0.21), but not thereafter from 30 days to 3 years (HR 1.01). These results are in accordance with the VANQWISH study (60) and the TIMI IIIB (61) trial showing no benefit from an early routine "invasive approach" after NQWMI. Nevertheless, the early benefit of ICP indicates that when a "conservative strategy" guided by ischemia approach is adopted, early ICP in NQWMI patients is beneficial.

The outcome of patients excluded from ART because of late arrival or other reasons did not differ significantly from patients treated with ART. The former are older, and more likely to be women (54) with other unfavorable characteristics that may influence their outcome. In these patients the use of ART 12 to 24 h after symptom onset is of limited benefit (58).

In this survey the "conservative strategy" of "watchful waiting" with coronary arteriography followed by mechanical reperfusion was associated with a decrease in early mortality (OR 0.53), but not thereafter, indicating a greater benefit with ICP when performed early. On the other hand, the higher use of ICP in hospitals with on-site catheterization facilities was not translated into a better outcome, and mortality rates in hospitals with and without such facilities were similar, in accordance with reports from other registries (20,38,62,63) and randomized trials (39,40). These findings may be explained by the fact that in Israel high risk patients can be transferred within a reasonable time to a tertiary center for coronary arteriography and revascularization. However, rapid availability, timing of intervention and other logistic problems should be considered. Also, we assume that some patients, especially those who were hospitalized in centers without on-site catheterization facilities, underwent such procedures after discharge as was noted in a more recent survey of our group (64), thus minimizing the early advantage obtained with the use of ICP during the index hospitalization.

Study limitations. The patients in this cohort were derived from a prospective nationwide survey performed during a two-month period in 1994. The decision whether to treat patients with ART and/or ICP was left to the discretion of the treating physician in each center, was not randomized and thus may have been influenced by differences in patients' baseline characteristics and physician bias, thus resulting in the selection of less severely ill patients. Despite multiple adjustment, we cannot conclude firmly that differences in prognosis in this study were due mainly to different treatment strategies, although their impact on prognosis seems very plausible. Despite these limitations, this study is based on an unselected population, and provides information on how the recommendations assessed from large randomized trials are implemented in daily clinical practice and their impact on early and long-term prognosis.

The present study includes data on in-hospital complications and long-term (3-year) mortality, but not morbidity data such as recurrent infarction, hospitalization for unstable angina, heart failure and need for angioplasty or CABG after discharge. We cannot exclude the possibility that even though the mortality was lower in patients treated with ART, their postdischarge morbidity may not have differed from those who were not reperfused. It is also possible that some patients underwent ICP after discharge, especially in centers without such facilities, which may influence their subsequent outcome.

Conclusions and clinical implications. This nationwide survey in unselected AMI patients hospitalized in CCUs demonstrates the extent of implementation in daily practice of ART and ICP proven to be effective in clinical trials, and their impact on short- and long-term prognosis after AMI. Acute reperfusion therapy (mainly thrombolysis), used in half of the patients, was associated with a trend for lower early mortality, but with significantly decreased long-term mortality, with a difference that amplified beyond the early postinfarction period, with an extended mortality benefit after 30 days through three years. The prognosis of patients not treated with ART differed according to the reason for exclusion, where patients with contraindication to ART carried the worst prognosis. Since the frequency of the use of thrombolytic therapy in this survey was quite high (44%), and could not be increased significantly, it seems reasonable that increase in the use of primary angioplasty, especially in patients with a contraindication to thrombolysis, may further reduce mortality of AMI patients. After ART, subsequent in-hospital use of ICP was relatively low as the result of the "conservative strategy" of "watchful waiting" with coronary arteriography followed by mechanical reperfusion, which was independently associated with a favorable early prognosis. Larger surveys and studies from different countries are needed to evaluate the outcome of patients treated with "conservative" or "invasive" strategy after AMI.

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